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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/824,627 | 04/14/2004 | Renata Pasqualini | UTSC:858US | 6275 |

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| EXAMINER | |
|---|---|
| POPA, ILEANA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/824,627 | PASQUALINI ET AL. | |
| | Examiner | Art Unit | |
| | Ileana Popa | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *25-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 1-24, and 39 have been cancelled.

Claims 25-38 are pending and under examination.

### *Response to Arguments*

### *Claim Rejections - 35 USC § 112*

3. The rejection of claim 15 under 35 U.S.C. 112, second paragraph, as being indefinite is moot because Applicant cancelled the claim in the response filed on 03/27/2007.

4. The rejection of claim 34 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's arguments filed on 03/27/2007.

### *Claim Rejections - 35 USC § 103*

4. The rejections of claims 2-7, 9-16, 21-23 under 35 U.S.C. 103(a) as being unpatentable over Harlow et al. (Antibodies: A Laboratory Manual, 1988), in view of Jat et al. (Proc Natl Acad Sci USA, 1991, 88: 5096-5100), Kano (JP62195296), and Kanki (Hybridoma, 1994, 13: 327-330) and over Jat et al., Kano, and Kanki, as applied to

claims 2-7, 9-16, 21-23, in further view of Green (J Immunol Meth, 1999, 231: 11-23) are moot because Applicant cancelled the claim in the response filed on 03/27/2007.

5. The rejection of claims 25-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow et al. taken with Jat et al., Kano, and Kanki, as applied to claims 2-7, 9-16, 21-23, in further view of Green (J Immunol Meth, 1999, 231: 11-23) is withdrawn in response to Applicant's arguments filed on 03/27/2007.

***New Rejections***

***Claim Rejections - 35 USC § 112, enablement***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 25-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating an antibody-producing cell by isolating antibody producing cells from a mouse obtained by transcrossing the Xenomouse with the Immotromouse, wherein the cells are isolated following the administration of an antigen to the mouse, does not reasonably provide enablement for a method of generating an antibody-producing cell by obtaining an antibody-producing cell that conditionally expresses a transforming oncogene and expresses the genetic component of human antibody production and contacting the cell with the desired antigen to produce human antibodies. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The instant claims, as written, encompass generating an antibody-producing cell by isolating a cell capable of producing antibodies, wherein the cell conditionally expresses a transforming oncogene and expresses the genetic component of human antibody production and wherein the cell is contacted with the antigen *in vitro* to generate antibodies. The art does not teach, and the specification does not disclose such a method of producing antibodies. One of skill in the art would readily recognize that antibodies could be produced by simply contacting a cell capable of producing antibodies with an antigen *in vitro*. In conclusion, the claims are not enabled to their full scope.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 25-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green (J Immunol Meth, 1999, 231: 11-23, of record), in view of both Kano (JP62195296, of record), Jat et al. (Proc Natl Acad Sci USA, 1991, 88: 5096-5100, of record), and Lidington et al. (Am J Physiol Cell Physiol, 2002, 282: C67-C74).

Green teaches the Xenomouse, wherein the Xenomouse comprises antibody-producing cells expressing the genetic complement of human antibody production and wherein the Xenomouse generates high affinity human monoclonal antibodies suitable to be used as therapeutics in humans when immunized with an antigen (claims 25 and 37) (Abstract, p. 12, column 2, first full paragraph, p. 13, column 1, second and third paragraphs, p. 20, columns 1 and 2). Although Green teaches that the Xenomouse offers flexibility, allowing the production of monoclonal antibodies either directly from hybridoma, from recombinant cell lines, or from transgenic animals (p. 19, column 2, second full paragraph), he does not specifically teach obtaining recombinant cell-lines by using the ts58A SV40 temperature sensitive mutant (claims 25-27). The use of immortalized recombinant cell lines to obtain monoclonal antibodies was known in the prior art. For example, Kano teaches the use of SV40 DNA to immortalize antigen-primed splenocytes for the production of stable monoclonal antibody-producing B-cells

(claim 33) (Abstract). Clearly the prior art teaches direct immortalization of B-cells using oncogenes such as the SV40 T antigen as an alternative approach to generate immortalized B-cell lines for the production of monoclonal antibodies. Kano doews not teach ts58A SV40 (claims 25-27). However, this is not innovative over the prior art, since the prior art teaches the use and the advantage of using ts58A SV40 to conditionally immortalize various cell lines to overcome immortalization-induced of loss differentiated characteristics (see for example Lidington et al., p. C67, column 2). In addition to the above, Jat et al. teach that immortalization *ex vivo* is complex and unpredictable and that the use of Immortomouse (i.e., a mouse harboring ts58A in its genome) overcomes the disadvantages of *ex vivo* immortalization because it facilitates and it ensures the presence of the conditional oncogene in all cells, at a common integration site and therefore, consistent derivatization of cell lines with the same characteristics (p. 5096, column 1 and 2, p. 5100, column 1 last paragraph). Based on all the teachings above, it would have been obvious to one of skill in the art, at the time the invention was made, to introduce the genetic background of the Immortomopuse into the genome of the Xenomouse, with a reasonable expectation of success. One of skill in the art would have been motivated to use ts58A because the art teaches the usefulness of obtaining a conditionally immortalized cell line (see above). One of skill in the art would have been motivated to introduce ts58A into the genomic background of the Xenomouse because the art teaches that such a method results in consistent derivatization of cells with the same characteristics (see above). One of skill in the art would readily recognize this as being a straightforward method to produce monoclonal

antibodies in the absence of hybridoma formation, which is a tedious process (claim 36). One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the use of intercrossing to introduce ts58A into the genetic background of genetically modified mice (see Lidington et al., p. C67 bridging p. C68, p. C73 bridging p. C74). With respect to the limitation recited in claims 28-30, Jat et al. teach that in order to derive immortal cell lines, the permissive temperature for growth is 33˚C (p. 5096, column 2). The limitations recited in claims 31, 32, 34, 35, and 38, these are not innovative over the prior art. Isolation of clones and antibody purification is routine in the production of monoclonal antibodies.(claims 31 and 38). One of skill in the art would have known to combine different clones to produce polyclonal antibodies, as needed (claim 32). One of skill in the art would have known to select the appropriate source of antigen (claims 34 and 35). Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

10. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

Joe Woitach
AU1633